

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
**WASHINGTON, D.C. 20460**



**OFFICE OF CHEMICAL SAFETY AND  
 POLLUTION PREVENTION**

**OPP OFFICIAL RECORD  
 HEALTH EFFECTS DIVISION  
 SCIENTIFIC DATA REVIEWS  
 EPA SERIES 361**


**MEMORANDUM**

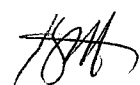
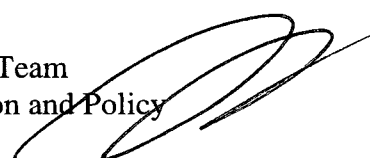
**DATE:** November 22, 2010

**SUBJECT:** *EPTC (CARBAMOTHIOIC ACID, DIPROPYL-, S-ETHYL  
 ESTER)* - Report of the OPP Endocrine Disruptor Review  
 Team - Test Order #: EDSP - 041401-64

**PC Code:** 041401  
**Decision No.:** N/A  
**Petition No.:** N/A  
**Risk Assessment Type:** N/A  
**TXR No.:** 0055433  
**MRID No.:** See Section V

**DP Barcode:** D375859 and D375860  
**Registration No.:** N/A  
**Regulatory Action:** N/A  
**Case No.:** N/A  
**CAS No.:** N/A  
**40 CFR:** N/A

**FROM:** Greg Akerman, Ph.D.   
 Executive Secretary  
 Endocrine Disruptor Review Team

**THROUGH** Karen Whitby, Ph.D., Co-Chair   
 Endocrine Disruptor Review Team  
 Office of Pesticide Programs  
 And  
 Gary Timm, Co-Chair  
 Endocrine Disruptor Review Team  
 Office of Science Coordination and Policy 

**TO:** Carissa Cyran  
 Chemical Review Manager  
 Pesticide Re-evaluation Division

**SUMMARY CONCLUSIONS**

Please find below a table that summarizes the Agency's conclusions regarding the submissions provided by the test order recipient and the public in response to the Agency's Test Order for the screening assays included in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery.

*Rec'd in RAC  
 11/24/2010  
 EW*

The table below summarizes the initial response of the test order recipient(s) as well as the conclusions of the Office of Chemical Safety and Pollution Prevention (OCSPP) Endocrine Disruptor Review Team (EDRT).

Chemical: EPTC 890 990			PC Code: 041401		
Test Order Recipient Response			Agency's Conclusions		
Guideline	Assay	Will Generate New Data	Existing Data Cited	Does Cited Data Satisfy the Order	Rationale
890.1100	Amphibian Metamorphosis Assay (Frog)	No	Yes	No	See Table 1 below.
890.1150	Androgen Receptor Binding (Rat Prostate)	No	Yes	No	See Table 2 below.
890.1200	Aromatase Assay (Human Recombinant)	No	Yes	No	See Table 3 below.
890.1250	Estrogen Receptor Binding	No	Yes	No	See Table 4 below.
890.1300	Estrogen Receptor Transcriptional Activation (Human Cell Line HeLa-9903)	No	Yes	No	See Table 5 below.
890.1350	Fish Short-Term Reproduction	No	Yes	No	See Table 6 below.
890.1400	Hershberger (Rat)	No	Yes	No	See Table 7 below.
890.1450	Female Pubertal (Rat)	No	Yes	No	See Table 8 below.
890.1500	Male Pubertal (Rat)	No	Yes	No	See Table 9 below.
890.1550	Steroidogenesis (Human Cell Line – H295R)	No	Yes	No	See Table 10 below.
890.1600	Uterotrophic (Rat)	No	Yes	No	See Table 11 below.

N/A = Not applicable; the test order recipient has agreed to conduct this assay.

The test order recipient will need to conduct all of the Tier 1 EDSP 890 Series Guideline assays identified in the table above. For EPTC, the apparent primary mode of action is inhibition of the cholinesterase enzyme. Therefore, the Agency recommends that measures of red blood cell (RBC) and brain cholinesterase measures be made in the Tier 1 *in vivo* assays in addition to the Tier 1 Assay measurements. The purpose of this recommendation is to facilitate the interpretation of any potential study findings.

## **I. BACKGROUND**

On October 29, 2009, the Agency began to issue test orders for the initial list of chemicals to be tested in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery under authority provided in section 408(p)(5) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The EDSP Tier 1 screening data required to satisfy an order are due within 2 years of the date of issuance of the order. The policies and procedures the Agency will use for the initial screening of chemicals are described in FRN Vol. 74, No. 71 (April 15, 2009).

The Agency formed the Endocrine Disruptor Review Team (EDRT) to support OCSPP scientists in their review of “other scientifically relevant information”<sup>1</sup> that may be cited by test order recipients or the public in response to EDSP Tier 1 test orders. The EDRT provides a centralized venue for the review of OSRI submitted in response to the EDSP Tier 1 test orders issued under 408(p) of FFDCA to screen pesticide chemicals for their potential to interact with the estrogen; androgen and thyroid (EAT) hormonal systems. The goal of the EDRT is to reach consistent, transparent and defensible conclusions on responses to the test orders for existing data cited and submitted to the Agency which are believed to be sufficient to satisfy part or all of the EDSP Tier 1 Test Order data requirements.

## **II. WEIGHT OF EVIDENCE EVALUATION OF THE OSRI**

Section II of this document provides a summary of the Agency review of existing data cited as OSRI by either the test order recipient or the public. Existing data may include data previously submitted to the Agency in support of a registration decision believed to be relevant to one or more of the assays in the test order. The cited study and its supporting data were considered relative to the Tier 1 EDSP assay for which they were cited. The Part 158 test guideline studies cited as OSRI are listed in bibliography section (Section V) of this report. The Agency conducted a weight-of-evidence determination of the significance of the data cited as OSRI by all sources (i.e., either the test order recipient or the public). The synthesis of this analysis is presented in Section II which consists of eleven tables; there is a table for each of the eleven assays which comprise the Tier 1 EDSP battery. Studies evaluated by the Agency in drawing conclusions to accept or reject the OSRI rationale are

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<sup>1</sup> “Other scientifically relevant information” is information that informs the determination as to whether the substance may have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). OSRI may either be functionally equivalent to information obtained from the Tier 1 assays—that is, data from assays that perform the same function as EDSP Tier 1 assays—or may include data that provide information on a potential consequence or effect that could be due to effects on the estrogen, androgen or thyroid systems.

presented in the table for each of the respective assays along with the Agency's rationale for the decision.

The EDRT's evaluations of the existing data cited in the OSRI are presented below in the following tables. Each of the tables provides the citations for existing data submitted to the Agency that were considered by the EDRT in their decision making. EDRT determined whether the cited/submitted data received from Gowan Company (the test order recipient) provided an accepted scientific method or protocol (and any other information relevant) to satisfy the requirements of the Test Order.

Section III of this memorandum contains a table that summarizes the endocrine-related findings in the studies cited in the submissions by the test order recipient and the public that were considered in the EDRT's weight of evidence evaluation.

Section IV of this memorandum contains a table that lists studies cited in the submissions by the test order recipient and the public that were rejected in the EDRT's weight of evidence evaluation and provides the reasons for this decision.

Section V of this memorandum contains the bibliography of all cited data from all sources (test order recipient(s) and public responses).

**Table 1. Evaluation of Data Submitted in Relation to the Amphibian Metamorphosis Assay**

Chemical: EPTC				PC Code: 041401		
890.1100 - Amphibian Metamorphosis Assay (Frog)						
1. EDSP Assay Endpoints <sup>1</sup>						
Study Type / Literature Citation	MRID No.	Developmental Stage	Hind Limb Length	Snout-Vent Length	Wet Body Weight	Thyroid Histopathology
Avian reproduction – mallard duck	46554301	--	--	--	--	--
Avian reproduction – bobwhite quail	46554302	--	--	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	--	--	--	--	--
1985- Two-Generation Reproduction - Rats	00161597	--	--	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--	--	--
1983- Developmental Toxicity - Rat	00138919	--	--	--	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--	--	--	--
1987-Developmental Toxicity – Rabbit	40442302	--	--	--	--	--
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--	--	--	X
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--	--	--	X

**Table 1. Evaluation of Data Submitted in Relation to the Amphibian Metamorphosis Assay**

Chemical: EPTC		PC Code: 041401				
890.1100 - Amphibian Metamorphosis Assay (Frog)						
Carcinogenicity – Mouse	00161596	--	--	--	--	x
1986-Chronic Toxicity – Dog	00161595	--	--	--	--	x
1987-Chronic Toxicity – Dog	40442301	--	--	--	--	x
Subchronic Oral Toxicity - Rat	00144651	--	--	--	--	x
Subchronic Oral Toxicity - Dog	00150327	--	--	--	--	x
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--	--	--
2. Summary of Study Findings:						
Study Type / Literature Citation	MRID No.	Findings				
Avian reproduction – mallard duck	46554301	Following exposure to EPTC, a significant reduction in the proportion of viable embryos to eggs set was observed at 593 and 1490 mg ai/kg dietary concentrations. At the highest concentration level (1490 mg ai/kg diet), significant adverse effects were observed on the number of eggs laid (p<0.01); eggs set (p<0.05); viable embryos (p<0.001); live embryos (p<0.001); number hatched (p<0.001); ratios of viable embryos to eggs set (p<0.01), number hatched to eggs laid (p<0.001) and to eggs set (p<0.001), hatchling survival (p<0.001) and the ratio of hatchling survivors to eggs set (p<0.01). The NOAEC was 242 mg ai/kg diet.				
Avian reproduction – bobwhite quail	46554302	Following exposure to EPTC, significant adverse effects were observed on several reproductive parameters at the highest treatment level (1490 mg ai/kg diet), including eggs cracked (p<0.05), the proportion of eggs not cracked to eggs laid (p<0.05), the proportion of eggs set to eggs laid (p=0.001), viable embryos (p<0.05) and live embryos (p<0.05). The NOAEC was 591 mg ai/kg diet.				

**Table 1. Evaluation of Data Submitted in Relation to the Amphibian Metamorphosis Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1100 - Amphibian Metamorphosis Assay (Frog)</b>		
1982- Two-Generation Reproduction - Rat	00121284	No effects were observed in the reproductive performances (male or female fertility indices, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio). No treatment-related changes were seen in absolute or relative weights of the testes and epididymides in any generation. No treatment-related histopathological lesions were seen in the testes, epididymides, spermatic cord, seminal vesicle, coagulating gland, prostate, urethra, bulbo-urethral gland, ovaries, oviduct, uterus, cervix and vagina in the offspring of either generation.
1985- Two-Generation Reproduction - Rats	00161597	No treatment-related effects were observed in male or female fertility indices, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio. Organ weights were not evaluated. No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle, prostate, ovaries, uterus, and vagina.
Developmental Neurotoxicity - Rat	46319101	There was no effect on reproductive performance in the mean numbers of live fetuses, resorptions, fetal body weights, or fetal sex ratios. No effects were reported in gestation length, viability, or lactation indices. Treatment had no effect on the mean age of attainment of vaginal opening for females or preputial separation for males.
1983- Developmental Toxicity - Rat	00138919	No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. There was an increase in post implantation loss and the subsequent reductions in the mean number of viable fetuses at the high dose.
1985 -Developmental Toxicity - Rat	00161598	No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. The pregnancy rate was 76%, 76% and 72% at the low-, mid- and high dose groups as compared to controls (84%). The decrease in the pregnancy rate is the result of increased post implantation loss at the mid (6.8%) and high (5.3%) dose groups when compared to controls (2.5%) with the increase reaching statistical significance ( $p < 0.05$ ) only for the mid-dose.
1985-Developmental Toxicity - Rabbit	00161599	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1987-Developmental Toxicity - Rabbit	40442302	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal

**Table 1. Evaluation of Data Submitted in Relation to the Amphibian Metamorphosis Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1100 - Amphibian Metamorphosis Assay (Frog)</b>		
		sex ratio, or soft tissue abnormalities at any dose.
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	No treatment-related changes were seen in absolute or relative weights of the thyroid, adrenal or pituitary glands at any dose level. No treatment-related histopathological lesions were seen in the thyroid, adrenal or pituitary glands at any dose level.
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	No treatment-related histopathological lesions were seen in the thyroid, adrenal or pituitary glands at any dose level.
Carcinogenicity – Mouse	00161596	Organ weights were not evaluated. No treatment-related histopathological lesions were seen in the thyroid, adrenal or pituitary glands at any dose level.
1986-Chronic Toxicity – Dog	00161595	No treatment-related changes were seen in absolute or relative weights of the thyroid, adrenal or pituitary glands at any dose level. No treatment-related histopathological lesions were seen in the thyroid, adrenal or pituitary glands at any dose level.
1987-Chronic Toxicity – Dog	40442301	No treatment-related changes were seen in absolute or relative weights of the thyroid, adrenal or pituitary glands at any dose level. No treatment-related histopathological lesions were seen in the thyroid, adrenal or pituitary glands at any dose level.
Subchronic Oral Toxicity - Rat	00144651	No treatment-related histopathological lesions were seen in the thyroid, adrenal and pituitary glands at any dose level.
Subchronic Oral Toxicity - Dog	00150327	No treatment-related changes were seen in absolute or relative weights of the thyroid gland at any dose level. No treatment-related histopathological lesions were seen in the thyroid, adrenal and pituitary glands at any dose level.
Subchronic Inhalation Toxicity – Rat	00154784	No treatment-related changes were seen in absolute or relative weights of the adrenal gland. Endocrine relevant organs were not examined microscopically. Histopathology was limited to nasal passages, liver, kidney and target tissues.
<b>3. Agency's Evaluation of the OSRI:</b> The submission provided by the test order recipient states that “The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program.		

**Table 1. Evaluation of Data Submitted in Relation to the Amphibian Metamorphosis Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1100 - Amphibian Metamorphosis Assay (Frog)</b>	
<p>The relevant regulatory studies include reproduction studies in rats and birds, multiple developmental studies in rats, rabbits and long-term studies in rats, mice and dogs. The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress.” “Thyroid hormone, T3 and T4, synthesis and secretion in the thyroid gland is regulated by a sensitive feedback mechanism that responds to the changes in circulating levels of thyroid hormones.” “According to EPA (Hill <i>et al.</i>, 1998), ‘treatments of rodents that cause <i>thyroid-pituitary disruption</i> result in chronic reduction in circulating thyroid hormone levels, increase in TSH levels and the development of increased cell division, increased size and numbers of thyroid cells, increased thyroid gland weight and, finally, tumors of the thyroid.’” “Thyroid weight provides a relative measure of its stimulation by TSH; thus, thyroid hormone levels are altered subtly, thyroid weight may reflect a change. Thyroid histopathology may provide a more sensitive indicator of this process.” “OECD implies that if the biological change does not take place, the alteration of T3, T4 or TSH has little biological relevance. As noted above, T3 and T4 levels are delicately regulated and the small persistent changes that result in disruption of thyroid hormone homeostasis leads to alterations in colloid area and follicular cell height. These will be readily evident in any histopathological analysis.” “This effect was not observed in any EPTC study. Likewise, no changes in thyroid weights were present in the rat, dog or mouse studies of any duration.”</p> <p>“Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCA section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery.”</p> <p>On review of the data cited as OSRI, the Agency noted a deficiency and therefore has outstanding questions about the potential for EPTC to interact with the HPT axis:</p>	

**Table 1. Evaluation of Data Submitted in Relation to the Amphibian Metamorphosis Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1100 - Amphibian Metamorphosis Assay (Frog)</b>	
<ul style="list-style-type: none"> <li>• In response to the test order recipient's focus in the OSRI statement on effects in humans, data required under the order provides information relevant to assessing the risks to fish and wildlife as well as human health. Background information on the development of the screening program, including information on screening for potential disruption of estrogen, androgen and thyroid in human, fish and wildlife, can be found at FRN Vol. 74, No. 71 (April 15, 2009).</li> <li>• The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>• The cited data do not demonstrate that exposure to EPTC caused any changes in the weight or histopathology of the thyroid gland in mammalian species. However, it is not readily apparent that the thyroid histopathology in the cited studies was conducted in the manner recommended by the EDSP Tier 1 guidelines for the Amphibian Metamorphosis Assay or the Pubertal Assays. These guidelines recommend a 5 point grading scale for examination of follicular cell height and colloid area. These instructions include photomicrographs as reference. The 5 point grading scale provides for evaluation of subtle changes that may improve the sensitivity of the histopathological examination.</li> <li>• However, a lack of effects in mammalian <i>in vivo</i> studies cited does not necessarily demonstrate the absence of interaction with the thyroid in other species. The complexity of the thyroid axis in amphibians yields many different possible mechanisms of inhibiting metamorphic processes at differing biochemical and molecular levels. Thus, changes seen in metamorphosis from interference with the thyroid axis, especially those involving effects in peripheral tissues may be pronounced in nonmammalian species, and therefore may not be apparent in mammalian assays.</li> </ul>	
<b>4. Conclusion:</b> Based on the deficiencies listed above, the data cited as OSRI did not satisfy the requirement for the Amphibian Metamorphosis Assay using Guideline 890.1100.	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 2. Evaluation of Data Submitted in Relation to the Androgen Receptor Binding Assay**

Chemical: EPTC		PC Code: 041401			
890.1150 - Androgen Receptor Binding Assay (Rat Prostate)					
1. EDSP Assay Endpoints <sup>1</sup>					
Study Type / Literature Citation	MRID No.	Binding Curve fit to Hills four-parameters are:			
		Top	Bottom	Slope	Log (IC <sub>50</sub> )
ToxCast program	N/A	--	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	--	--	--	--
1985- Two-Generation Reproduction - Rats	00161597	--	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--	--
1983- Developmental Toxicity - Rat	00138919	--	--	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--	--	--
1987-Developmental Toxicity – Rabbit	40442302	--	--	--	--
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--	--	--
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--	--	--
Carcinogenicity – Mouse	00161596	--	--	--	--
1986-Chronic Toxicity – Dog	00161595	--	--	--	--
1987-Chronic Toxicity – Dog	40442301	--	--	--	--
Subchronic Oral Toxicity - Rat	00144651	--	--	--	--
Subchronic Oral Toxicity - Dog	00150327	--	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--	--
2. Summary of Study Findings:					
Study Type / Literature Citation	MRID No.	Findings			
ToxCast program	N/A	See discussion below in Section 3.			
Part 158 studies cited above	See Above	The cited <i>in vivo</i> Part 158 mammalian toxicity studies do not measure binding of the chemical to the androgen receptor.			

**Table 2. Evaluation of Data Submitted in Relation to the Androgen Receptor Binding Assay****Chemical: EPTC****PC Code: 041401****890.1150 - Androgen Receptor Binding Assay (Rat Prostate)****3. Agency's Evaluation of the OSRI:**

The submission provided by the test order recipient states that "The Agency developed the ToxCast<sup>TM</sup> program to predict endocrine active agents and profiled over 300 chemicals including EPTC. ToxCast results indicated EPTC has a very low potential for endocrine disruption."

"The EPTC studies collectively evaluate nearly all relevant biological endpoints of estrogen or androgen mediation of the HPG axis. Multiple studies address most of the endpoints of concern. The few endpoints not directly evaluated are associated with multiple adverse effects; these other effects would have been evident in the regulatory studies from the other monitored parameters."

"The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program." "The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress." "Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCFA section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery."

On review of the OSRI submitted, the Agency noted a number of deficiencies and therefore has outstanding questions about the potential for EPTC to interact with the androgen receptor.

- Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast *in vitro* assays cannot at this time be

**Table 2. Evaluation of Data Submitted in Relation to the Androgen Receptor Binding Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1150 - Androgen Receptor Binding Assay (Rat Prostate)</b>	
<p>considered acceptable alternatives to the EDSP Tier 1 <i>in vitro</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Androgen Receptor Binding Assay using Guideline 890.1150 (Kavlock and Zenick, 2010).</p> <ul style="list-style-type: none"> <li>• The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>• None of the cited Part 158 studies measure binding of the chemical to the androgen receptor (AR), which is the information that would be obtained by the Tier 1 AR Binding Assay. There was no substantive explanation explaining why the lack of any effect in these studies should be considered evidence that binding to the androgen receptors does not occur in non-mammalian species. A lack of effects on potentially receptor-mediated endpoints in the mammalian <i>in vivo</i> studies cited does not necessarily demonstrate the absence of an interaction with the receptors in other species. Because chemicals that bind to a receptor but do not cause an effect in mammals may nevertheless show effects in other species, it is important to have information concerning direct interaction with the androgen receptor.</li> </ul>	
<p><b>Conclusion:</b> Based on the deficiencies discussed above, the data cited as OSRI did not satisfy the requirement for the Androgen Receptor Binding Assay using Guideline 890.1150.</p>	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 3. Evaluation of Data Submitted in Relation to the Aromatase (Human Recombinant) Assay**

Chemical: EPTC		PC Code: 041401	
890.1200 - Aromatase Assay (Human Recombinant)			
1. EDSP Assay Endpoints <sup>1</sup>			
Study Type / Literature Citation	MRID No.	<sup>3</sup> H <sub>2</sub> O measured	Estrone measured
ToxCast program	N/A	--	--
1982- Two-Generation Reproduction - Rat	00121284	--	--
1985- Two-Generation Reproduction - Rats	00161597	--	--
Developmental Neurotoxicity - Rat	46319101	--	--
1983- Developmental Toxicity - Rat	00138919	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--
1987-Developmental Toxicity – Rabbit	40442302	--	--
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--
Carcinogenicity – Mouse	00161596	--	--
1986-Chronic Toxicity – Dog	00161595	--	--
1987-Chronic Toxicity – Dog	40442301	--	--
Subchronic Oral Toxicity - Rat	00144651	--	--
Subchronic Oral Toxicity - Dog	00150327	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--
2. Summary of Study Findings:			
Study Type / Literature Citation	MRID No.	Findings	
ToxCast program	N/A	See discussion below in Section 3.	
Part 158 studies cited above	See Above	The cited <i>in vivo</i> Part 158 mammalian toxicity studies do not measure Aromatase activity.	

**Table 3. Evaluation of Data Submitted in Relation to the Aromatase (Human Recombinant) Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1200 - Aromatase Assay (Human Recombinant)</b>	
<p><b>3. Agency's Evaluation of the OSRI:</b></p> <p>The submission provided by the test order recipient states that "The Agency developed the ToxCast™ program to predict endocrine active agents and profiled over 300 chemicals including EPTC. ToxCast results indicated EPTC has a very low potential for endocrine disruption."</p> <p>"The EPTC studies collectively evaluate nearly all relevant biological endpoints of estrogen or androgen mediation of the HPG axis. Multiple studies address most of the endpoints of concern. The few endpoints not directly evaluated are associated with multiple adverse effects; these other effects would have been evident in the regulatory studies from the other monitored parameters."</p> <p>"Serum cholesterol is of particular importance as cholesterol is a molecular precursor of all steroid hormones in humans, including estrogens and androgens. Early disruption of steroidogenesis can lead to altered levels of cholesterol and disruptions in cholesterol synthesis can affect steroidogenesis. Cholesterol levels were unaffected in all studies in which it was measured including both male and female rats (90 day oral and inhalation studies and two year studies), and dogs (90 day and one-year studies)."</p> <p>"The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program." "The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCA section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery."</p>	

**Table 3. Evaluation of Data Submitted in Relation to the Aromatase (Human Recombinant) Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1200 - Aromatase Assay (Human Recombinant)</b>	
<p>On review of the OSRI submitted, the Agency noted a number of deficiencies and therefore has outstanding questions about the potential for EPTC to interact with the Aromatase enzyme.</p> <ul style="list-style-type: none"> <li>• Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vitro</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Aromatase Assay using Guideline 890.1200 (Kavlock and Zenick, 2010).</li> <li>• Cholesterol is the building block for the synthesis of all of the steroid hormones. A change in the synthesis of testosterone or estrogen would not necessarily be reflected in differential levels of cholesterol and this would be an insensitive measure for such downstream events.</li> <li>• The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>• None of the cited Part 158 studies measure aromatase activity, which is the information that would be obtained by the Tier 1 Aromatase Assay. The argument presented in the explanations submitted to the Agency was that no aromatase-mediated effects were seen in any of the cited studies. Aromatase is required for the conversion of androgens to estrogens. The available/cited data do not permit the Agency to establish confident linkages between effects on apical endpoints measured in whole animal studies and inhibition of aromatase enzyme activity.</li> </ul>	
<p><b>4. Conclusion:</b> Based on the deficiency discussed above, the data cited as OSRI did not satisfy the requirement for the Aromatase Assay using Guideline 890.1200.</p>	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 4. Evaluation of Data Submitted in Relation to the Estrogen Receptor Binding Assay**

Chemical: EPTC		PC Code: 041401			
890.1250 - Estrogen Receptor Binding Assay					
1. EDSP Assay Endpoints <sup>1</sup>					
Study Type / Literature Citation	MRID No.	Binding Curve fit to Hills four-parameters are:			
		Top	Bottom	Slope	Log(IC <sub>50</sub> )
ToxCast program	N/A	--	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	--	--	--	--
1985- Two-Generation Reproduction - Rats	00161597	--	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--	--
1983- Developmental Toxicity - Rat	00138919	--	--	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--	--	--
1987-Developmental Toxicity – Rabbit	40442302	--	--	--	--
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--	--	--
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--	--	--
Carcinogenicity – Mouse	00161596	--	--	--	--
1986-Chronic Toxicity – Dog	00161595	--	--	--	--
1987-Chronic Toxicity – Dog	40442301	--	--	--	--
Subchronic Oral Toxicity - Rat	00144651	--	--	--	--
Subchronic Oral Toxicity - Dog	00150327	--	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--	--
2. Summary of Study Findings:					
Study Type / Literature Citation	MRID No.	Findings			
ToxCast program	N/A	See discussion below in Section 3			
Part 158 studies cited above	See Above	The cited <i>in vivo</i> Part 158 mammalian toxicity studies do not measure binding of the chemical to the estrogen receptor			

**Table 4. Evaluation of Data Submitted in Relation to the Estrogen Receptor Binding Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1250 - Estrogen Receptor Binding Assay</b>	
<p><b>3. Agency's Evaluation of the OSRI:</b></p> <p>The submission provided by the test order recipient states that "The Agency developed the ToxCast™ program to predict endocrine active agents and profiled over 300 chemicals including EPTC. ToxCast results indicated EPTC has a very low potential for endocrine disruption."</p> <p>"The EPTC studies collectively evaluate nearly all relevant biological endpoints of estrogen or androgen mediation of the HPG axis. Multiple studies address most of the endpoints of concern. The few endpoints not directly evaluated are associated with multiple adverse effects; these other effects would have been evident in the regulatory studies from the other monitored parameters."</p> <p>"The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program." "The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCA section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery."</p> <p>On review of the OSRI submitted, the Agency noted a number of deficiencies and therefore has outstanding questions about the potential for EPTC to interact with the Estrogen Receptor.</p>	

**Table 4. Evaluation of Data Submitted in Relation to the Estrogen Receptor Binding Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1250 - Estrogen Receptor Binding Assay</b>	
<ul style="list-style-type: none"> <li>Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vitro</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Estrogen Receptor Binding Assay using Guideline 890.1250 (Kavlock and Zenick, 2010).</li> <li>The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>None of the cited Part 158 studies measure binding of the chemical to the estrogen receptor (ER), which is the information that would be obtained by the Tier 1 ER binding assay. The argument presented in the explanations submitted to the Agency was that no estrogenic effects were seen in any of the cited studies. There was no substantive explanation explaining why the lack of any effect in these studies should be considered evidence that binding to the estrogen receptors does not occur. A lack of effect on potentially receptor-mediated endpoints in the mammalian <i>in vivo</i> studies cited does not necessarily demonstrate the absence of an interaction with the receptors in other species. Because chemicals that bind to a receptor but do not cause an effect in mammals may nevertheless show effects in other species, it is important to have information concerning direct interaction with the estrogen receptor.</li> </ul>	
<b>4. Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Estrogen Receptor Binding Assay using Guideline 890.1250.	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 5. Evaluation of Data Submitted in Relation to the Estrogen Receptor Transcriptional Activation Assay**

Chemical: EPTC		PC Code: 041401		
890.1300 - Estrogen Receptor Transcriptional Activation Assay (Human Cell Line HeLa-9903)				
1. EDSP Assay Endpoints <sup>1</sup>				
Study Type / Literature Citation	MRID No.	Bioluminescence measurements:		
		EC50	PC50	PC10
ToxCast program	N/A	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	--	--	--
1985- Two-Generation Reproduction - Rats	00161597	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--
1983- Developmental Toxicity - Rat	00138919	--	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--	--
1987-Developmental Toxicity – Rabbit	40442302	--	--	--
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--	--
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--	--
Carcinogenicity – Mouse	00161596	--	--	--
1986-Chronic Toxicity – Dog	00161595	--	--	--
1987-Chronic Toxicity – Dog	40442301	--	--	--
Subchronic Oral Toxicity - Rat	00144651	--	--	--
Subchronic Oral Toxicity - Dog	00150327	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--
2. Summary of Study Findings:				
Study Type / Literature Citation	MRID No.	Findings		
ToxCast program		See discussion below in Section 3		
Part 158 studies cited above	See Above	The cited <i>in vivo</i> Part 158 mammalian toxicity studies do not measure the potential of the chemical to transactivate the estrogen receptor.		

**Table 5. Evaluation of Data Submitted in Relation to the Estrogen Receptor Transcriptional Activation Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1300 - Estrogen Receptor Transcriptional Activation Assay (Human Cell Line HeLa-9903)</b>	
<p><b>3. Agency's Evaluation of the OSRI:</b></p> <p>The submission provided by the test order recipient states that "The Agency developed the ToxCast™ program to predict endocrine active agents and profiled over 300 chemicals including EPTC. ToxCast results indicated EPTC has a very low potential for endocrine disruption."</p> <p>"The EPTC studies collectively evaluate nearly all relevant biological endpoints of estrogen or androgen mediation of the HPG axis. Multiple studies address most of the endpoints of concern. The few endpoints not directly evaluated are associated with multiple adverse effects; these other effects would have been evident in the regulatory studies from the other monitored parameters."</p> <p>"The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program." "The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCa section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery."</p> <p>On review of the OSRI submitted, the Agency noted a number of deficiencies and therefore has outstanding questions about the potential for EPTC to transactivate ER.</p>	

**Table 5. Evaluation of Data Submitted in Relation to the Estrogen Receptor Transcriptional Activation Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1300 - Estrogen Receptor Transcriptional Activation Assay (Human Cell Line HeLa-9903)</b>	
<ul style="list-style-type: none"> <li>Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vitro</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Estrogen Receptor Transactivation Assay using Guideline 890.1300 (Kavlock and Zenick, 2010).</li> <li>The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>None of the cited Part 158 studies measure activation of estrogen-receptor-controlled DNA transcription, which is the information that would be obtained by the Tier 1 ER Transcriptional Activation Assay. The argument presented in the explanations submitted to the Agency was that no estrogenic effects were seen in any of the cited studies. There was no substantive explanation explaining why lack of measurement of ER-controlled transcriptional activation in these studies should be considered evidence that such an effect does not occur. A lack of effects on potentially receptor-mediated endpoints in the mammalian <i>in vivo</i> studies cited does not necessarily demonstrate that interaction with the receptors is absent. Because chemicals that bind to a receptor but do not cause an effect in mammals may nevertheless show effects in other species, it is important to have information concerning direct activation of estrogen-receptor-controlled DNA transcription.</li> </ul>	
<p><b>4. Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Estrogen Receptor Transcriptional Activation Assay using Guideline 890.1300.</p>	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 6. Evaluation of Data Submitted in Relation to the Fish Short-Term Reproduction Assay**

Chemical: EPTC					PC Code: 041401			
890.1350 - Fish Short-Term Reproduction								
1. EDSP Assay Endpoints <sup>1</sup>								
Study Type / Literature Citation	MRID No.	Reproductive Behavior and Secondary Sex Characteristics						
		Fecundity	Fertility	Vitellogenin	Sex Steroid Concentration	Secondary Sex Characteristics	Gonado-Somatic Index	Gonadal Histopathology
Avian reproduction – mallard duck	46554301	X	X	--	--	--	--	--
Avian reproduction – bobwhite quail	46554302	X	X	--	--	--	--	--
2. Summary of Study Findings:								
Study Type / Literature Citation	MRID No.	Findings						
Avian reproduction – mallard duck	46554301	Following exposure to EPTC, a significant reduction in the proportion of viable embryos to eggs set was observed at 593 and 1490 mg ai/kg dietary concentrations. At the highest concentration level (1490 mg ai/kg diet), significant adverse effects were observed on the number of eggs laid (p<0.01); eggs set (p<0.05); viable embryos (p<0.001); live embryos (p<0.001); number hatched (p<0.001); ratios of viable embryos to eggs set (p<0.01), number hatched to eggs laid (p<0.001) and to eggs set (p<0.001), hatchling survival (p<0.001) and the ratio of hatchling survivors to eggs set (p<0.01). The NOAEC was 242 mg ai/kg diet.						
Avian reproduction – bobwhite quail	46554302	Following exposure to EPTC, significant adverse effects were observed on several reproductive parameters at the highest treatment level (1490 mg ai/kg diet), including eggs cracked (p<0.05), the proportion of eggs not cracked to eggs laid (p<0.05), the proportion of eggs set to eggs laid (p=0.001), viable embryos (p<0.05) and live embryos (p<0.05). The NOAEC was 591 mg ai/kg diet.						
3. Agency's Evaluation of the OSRI:								
The submission provided by the test order recipient states that “The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program. The relevant regulatory studies include reproduction								

**Table 6. Evaluation of Data Submitted in Relation to the Fish Short-Term Reproduction Assay****Chemical: EPTC****PC Code: 041401****890.1350 - Fish Short-Term Reproduction**

studies in rats and birds, multiple developmental studies in rats, rabbits and long-term studies in rats, mice and dogs. The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. The absence of any effect on serum cholesterol in the whole-animal regulatory studies confirms that EPTC does not cause perturbation of steroidogenesis. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCa section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery."

On review of the OSRI submitted, the Agency noted a number of deficiencies and therefore has outstanding questions:

- Overall, the Part 158 [eco] data cited by the test order recipient indicate that EPTC exposure has the potential to affect apical endpoints of reproduction and development in birds. However, the studies lack sufficient information to determine whether or not and to what extent the reproductive and developmental effects are driven by endocrine-mediated processes potentially affected by EPTC exposure. None of the Part 158 studies cited in the OSRI measure vitellogenin, sex steroid concentrations, secondary sex characteristics, or gonadal-somatic index, which are included in the Fish-Short Term Reproduction Assay and are more diagnostic indicators of endocrine-interaction.
- The test order recipient cites a reference that states that inhibition of acetylcholinesterase (AChE) can cause thyroid and gonadal dysfunction. Cholinesterase measurements were not conducted in the avian reproduction studies. Moreover, evidence of cholinesterase inhibition alone is not sufficient to preclude the potential for interaction with the hypothalamic-pituitary-gonadal (HPG) axis.
- Although the endpoints of fecundity and fertility as measured in the avian reproduction studies fulfilled requirements for an avian reproduction test with EPTC in the diet, they are considered inadequate within the context of the Fish Short-Term Reproduction assay because the dietary route of exposure used in the avian studies is not necessarily informative of aquatic exposure effects in fish. EPTC consumed in the diet is

**Table 6. Evaluation of Data Submitted in Relation to the Fish Short-Term Reproduction Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1350 - Fish Short-Term Reproduction</b>	
subject to different metabolic processes and therefore could have different effects than EPTC absorbed through the gills and integument. Additionally, avian reproduction studies are unable to replicate the continuous exposure scenario of fish embryos and larvae.	
<b>4. Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Fish Short-Term Reproduction Assay using Guideline 890.1350.	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 7. Evaluation of Data Submitted in Relation to the Hershberger Assay**

Chemical: EPTC		PC Code: 041401				
890.1400 - Hershberger Assay						
1. EDSP Assay Endpoints <sup>1</sup>						
Study Type / Literature Citation	MRID No.	Tissue Weight				
		Ventral Prostate	Seminal Vesicle	LABC Muscle	Cowper's Glands	Glans Penis
ToxCast program	N/A	--	--	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	--	--	--	--	--
1985- Two-Generation Reproduction - Rats	00161597	--	--	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--	--	--
1983- Developmental Toxicity - Rat	00138919	--	--	--	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--	--	--	--
1987-Developmental Toxicity – Rabbit	40442302	--	--	--	--	--
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--	--	--	--
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--	--	--	--
Carcinogenicity – Mouse	00161596	--	--	--	--	--
1986-Chronic Toxicity – Dog	00161595	--	--	--	--	--
1987-Chronic Toxicity – Dog	40442301	--	--	--	--	--
Subchronic Oral Toxicity - Rat	00144651	--	--	--	--	--
Subchronic Oral Toxicity - Dog	00150327	--	--	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--	--	--
2. Summary of Study Findings:						
Study Type / Literature Citation	MRID No.	Findings				
ToxCast program	N/A	See discussion below in Section 3.				
1982 - Two-Generation Reproduction-Rat	00121284	No treatment-related effects were observed in reproductive performance (male fertility index or fetal sex ratio), absolute or relative organ weights (testes and epididymides), or histopathological lesions (testes,				

**Table 7. Evaluation of Data Submitted in Relation to the Hershberger Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1400 - Hershberger Assay</b>		
		epididymides, spermatic cord, seminal vesicle, coagulating gland or prostate) in the offspring of either generation.
1985 - Two-Generation Reproduction- Rats	00161597	No treatment-related effects were observed in male fertility, sex ratio, or histopathological lesions in the testes, epididymides, seminal vesicle or prostate of pups in either generation. Organ weights were not evaluated.
Developmental Neurotoxicity- Rat	46319101	There was no effect on reproductive performance in the mean numbers of corpora lutea, implantation, live fetuses, resorptions, fetal body weights, or fetal sex ratios. No effects were reported in gestation length, viability, or lactation indices. Treatment had no effect on the mean age of attainment of preputial separation for males.
1983 - Developmental Toxicity-Rat	00138919	No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. There was an increase in post implantation loss and the subsequent reductions in the mean number of viable fetuses at the high dose.
1985 - Developmental Toxicity-Rat	00161598	No treatment-related changes were seen in fetal sex ratio, or soft tissue abnormalities at any dose.
1985 - Developmental Toxicity – Rabbit	00161599	No treatment-related changes were seen in pregnancy rate, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1987 - Developmental Toxicity – Rabbit	40442302	No treatment-related changes were seen in number of implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	No treatment-related changes were seen in absolute or relative weights of the testes or histopathological lesions in the testes, epididymides or at any dose level.
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	No treatment-related changes were seen in absolute or relative weights of the testes or histopathological lesions in the testes, epididymides, seminal vesicle or prostate at any dose level.
Carcinogenicity – Mouse	00161596	Organ weights were not evaluated. No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle or prostate at

**Table 7. Evaluation of Data Submitted in Relation to the Hershberger Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1400 - Hershberger Assay</b>		
		any dose level.
1986 - Chronic Toxicity – Dog	00161595	No treatment-related changes were seen in absolute or relative weights of the testes or histopathological lesions in the testes or prostate at any dose level.
1987 - Chronic Toxicity – Dog	40442301	No treatment-related changes were seen in absolute or relative weights of the testes or histopathological lesions in the testes, epididymides, or prostate at any dose level.
Subchronic Oral Toxicity - Rat	00144651	No treatment-related changes in absolute or relative weights of the testes and histopathological lesions were seen in the testes, epididymides, seminal vesicle or prostate at any dose level.
Subchronic Oral Toxicity - Dog	00150327	No treatment-related changes were seen in absolute or relative weights of the testes and there were no treatment-related histopathological lesions in the testes, epididymides or prostate at any dose level.
Subchronic Inhalation Toxicity – Rat	00154784	No treatment-related changes were seen in absolute or relative weights of the testes. Endocrine relevant organs were not examined microscopically. Histopathology was limited to nasal passages, liver, kidney and target tissues.

**3. Agency's Evaluation of the OSRI:**

The submission provided by the test order recipient states that “The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program.” “The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. The absence of any effect on serum cholesterol in the whole-animal regulatory studies confirms that EPTC does not cause perturbation of steroidogenesis. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential

**Table 7. Evaluation of Data Submitted in Relation to the Hershberger Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1400 - Hershberger Assay</b>	
<p>endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCA section 408(p)(4).” “Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery.”</p> <p>On review of the OSRI submitted, the Agency noted deficiencies and therefore has outstanding questions about the potential for EPTC to disturb the HPG axis:</p> <ul style="list-style-type: none"> <li>• Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vivo</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Hershberger Assay using Guideline 890.1400 (Kavlock and Zenick, 2010).</li> <li>• The Hershberger assay and the cited OSRI differ in that the Hershberger assay includes a measurement of the weight of the ventral prostate and four tissues that are part of the male secondary sex organs (seminal vesicle, Cowper’s gland, LABC muscle complex, and glans penis). The cited studies do not provide data on the weights of any of these specific androgen responsive tissues.</li> <li>• The other major difference between the cited studies and the Hershberger assay is that the cited studies used intact animals. The Hershberger assay uses the castrated male rat in order to increase the sensitivity of the overall test system to androgen-mediated effects.</li> </ul> <p><b>4. Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Hershberger Assay using Guideline 890.1400.</p>	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

Chemical: EPTC					PC Code: 041401					
890.1450 - Female Pubertal Assay (Rat)										
1. EDSP Assay Endpoints <sup>1</sup>				Organ Weights						
Study Type / Literature Citation	MRID No.	Growth	Age and Weight at VO	Uterus	Ovaries	Thyroid	Liver	Kidneys	Pituitary	Adrenals
ToxCast program	N/A	--	--	--	--	--	--	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	X	--	--	--	--	X	X	--	--
1985- Two-Generation Reproduction - Rats	00161597	X	--	--	--	--	--	--	--	--
Developmental Neurotoxicity - Rat	46319101	X	X	--	--	--	--	--	--	--
1983- Developmental Toxicity - Rat	00138919	X	--	--	--	--	--	--	--	--
1985 -Developmental Toxicity - Rat	00161598	X	--	--	--	--	--	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	X	--	--	--	--	--	--	--	--
1987-Developmental Toxicity – Rabbit	40442302	X	--	--	--	--	--	--	--	--
1983-Chronic Toxicity/ Carcinogenicity – Rat	00145004	X	--	--	X	X	X	X	X	X
1987-Chronic Toxicity/ Carcinogenicity – Rat	40215001	X	--	--	X	--	X	X	--	--
Carcinogenicity – Mouse	00161596	X	--	--	--	--	--	--	--	--

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

Chemical: EPTC					PC Code: 041401					
890.1450 - Female Pubertal Assay (Rat)										
1986-Chronic Toxicity – Dog	00161595	X	--	--	X	X	X	X	X	X
1987-Chronic Toxicity – Dog	40442301	X	--	--	X	X	X	X	X	X
Subchronic Oral Toxicity - Rat	00144651	X	--	--	X	--	X	X	--	--
Subchronic Oral Toxicity - Dog	00150327	X	--	--	X	X	--	--	--	X
Subchronic Inhalation Toxicity – Rat	00154784	X	--	--	X	--	--	--	--	X
		Clinical Chemistry, Hormone, Pathology, Cyclicity <sup>1</sup>								
		Histopathology				Blood Chemistry	Hormones		Estrous Cyclicity (Age, Length & % of animals Cycling)	
		Uterus	Ovary	Thyroid	Kidney		T4	TSH		
ToxCast program	N/A	--	--	--	--	--	--	--	--	--
1982- Two-Generation Reproduction - Rat	00121284	X	X	--	X	--	--	--	--	--
1985- Two-Generation Reproduction - Rats	00161597	X	X	--	X	X	--	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--	--	--	--	--	--	--
1983- Developmental Toxicity - Rat	00138919	--	--	--	--	--	--	--	--	--
1985 -Developmental Toxicity - Rat	00161598	--	--	--	--	--	--	--	--	--
1985-Developmental Toxicity – Rabbit	00161599	--	--	--	--	--	--	--	--	--
1987-Developmental	40442302	--	--	--	--	--	--	--	--	--

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

Chemical: EPTC					PC Code: 041401				
890.1450 - Female Pubertal Assay (Rat)									
Toxicity – Rabbit									
1983-Chronic Toxicity/Carcinogenicity – Rat	00145004	X	X	X	X	X	--	--	--
1987-Chronic Toxicity/Carcinogenicity – Rat	40215001	X	X	X	X	X	--	--	--
Carcinogenicity – Mouse	00161596	X	X	X	X	--	--	--	--
1986-Chronic Toxicity – Dog	00161595	X	X	X	X	X	--	--	--
1987-Chronic Toxicity – Dog	40442301	X	X	X	X	X	--	--	--
Subchronic Oral Toxicity - Rat	00144651	X	X	X	X	X	--	--	--
Subchronic Oral Toxicity - Dog	00150327	X	X	X	X	X	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--	X	X	--	--	--
2. Summary of Study Findings:									
Study Type / Literature Citation	MRID No.	Findings							
ToxCast program	N/A	See discussion below in Section 3.							
1982 - Two-Generation Reproduction-Rat	00121284	No treatment-related effects were observed in female fertility index, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio. No treatment-related histopathological lesions were seen in the ovaries, uterus, cervix and vagina in the offspring of either generation.							
1985 - Two-Generation	00161597	No treatment-related effects were observed in female fertility indices, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio. No treatment-							

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1450 - Female Pubertal Assay (Rat)</b>		
Reproduction- Rats		related histopathological lesions were seen in the ovaries, uterus, and vagina. Organ weights were not evaluated.
Developmental Neurotoxicity - Rat	46319101	There was no effect on reproductive performance in the mean numbers of live fetuses, fetal body weights, or fetal sex ratios. No effects were reported in gestation length, viability, or lactation indices. Treatment had no effect on the mean age of attainment of vaginal opening for females.
1983 - Developmental Toxicity-Rat	00138919	No treatment-related changes were seen in pregnancy rate, numbers of corpora lutea, fetal sex ratio, or soft tissue abnormalities at any dose. There was an increase in post implantation loss and the subsequent reductions in the mean number of viable fetuses at the high dose.
1985 -Developmental Toxicity-Rat	00161598	No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. The pregnancy rate was 76%, 76% and 72% at the low-, mid- and high dose groups as compared to controls (84%). The decrease in the pregnancy rate is the result of increased post implantation loss at the mid (6.8%) and high (5.3%) dose groups when compared to controls (2.5%) with the increase reaching statistical significance ( $p < 0.05$ ) only for the mid-dose.
1985 -Developmental Toxicity – Rabbit	00161599	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1987 -Developmental Toxicity – Rabbit	40442302	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	No treatment-related changes were seen in absolute or relative weights of the ovaries, thyroid, adrenal or pituitary glands nor were there any treatment-related histopathological lesions in the ovaries, uterus, cervix, mammary, thyroid, adrenal or pituitary glands at any dose level.
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	No treatment-related changes were seen in absolute or relative weights of the ovaries or histopathological lesions in the ovaries, uterus, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level.
Carcinogenicity – Mouse	00161596	No treatment-related histopathological lesions were seen in the ovaries, uterus, cervix, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level. Organ weights were not evaluated.
1986 - Chronic Toxicity – Dog	00161595	No treatment-related changes were seen in absolute or relative weights of the ovaries, thyroid, adrenal or pituitary glands. No treatment-related histopathological lesions were seen in the ovaries, uterus, vagina, mammary glands, thyroid, adrenal or pituitary glands at any dose level.

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1450 - Female Pubertal Assay (Rat)</b>		
1987 - Chronic Toxicity – Dog	40442301	No treatment-related changes were seen in absolute or relative weights of the ovaries, thyroid, adrenal or pituitary glands nor were there any treatment-related histopathological lesions in the ovaries, uterus, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level.
Subchronic Oral Toxicity - Rat	00144651	No treatment-related changes were seen in absolute or relative weights of the ovaries and no treatment-related histopathological lesions were seen in the ovaries, uterus, cervix, vagina, mammary glands, thyroid, adrenal or pituitary glands at any dose level.
Subchronic Oral Toxicity - Dog	00150327	No treatment-related changes were seen in absolute or relative weights of the ovaries or thyroid glands. No treatment-related histopathological lesions were seen in the ovaries, uterus, cervix, thyroid, adrenal or pituitary glands at any dose level.
Subchronic Inhalation Toxicity – Rat	00154784	No treatment-related changes were seen in absolute or relative weights of the ovaries or adrenal glands. Endocrine relevant organs were not examined. Histopathology was limited to nasal passages, liver, kidney and target tissues.

**3. Agency's Evaluation of the OSRI:**

The submission provided by the test order recipient states that “The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program.” “The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. The absence of any effect on serum cholesterol in the whole-animal regulatory studies confirms that EPTC does not cause perturbation of steroidogenesis. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCa section 408(p)(4).” “Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery.”

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1450 - Female Pubertal Assay (Rat)</b>	
<p>On review of the OSRI submitted, the Agency noted deficiencies and has remaining questions about the potential for EPTC to disrupt the HPG and HPT axis in females:</p> <ul style="list-style-type: none"> <li>Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vivo</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Female Pubertal Assay using Guideline 890.1450 (Kavlock and Zenick, 2010).</li> <li>The female offspring in the Developmental Neurotoxicity (DNT) study were evaluated for acceleration or delay in vaginal opening; exposure of the test animals to EPTC had ceased by the time that this endpoint was evaluated. The Tier 1 Female Pubertal Assay exposes the animals during the period during which this endpoint is susceptible to chemical influence. No information was provided to show that ending exposure substantially prior to the normal age of sexual maturation is equivalent to dosing during the critical peri-pubertal period.</li> <li>None of the studies cited measured estrous cyclicity, which is an important indicator of interaction with the endocrine system.</li> <li>Organ weight data in the cited studies are inadequate because they were obtained in adult / older animals and so do not provide information on the potential for effects at the critical life stage, whereas in the Tier 1 Female Pubertal Assay, organ weights are obtained in pubertal /young animals.</li> <li>Histopathology data in the cited Part 158 studies are inadequate because they were obtained in adult /older animals and so do not provide information on the potential for effects at the critical life stage, whereas in the Tier 1 Female Pubertal Assay, histopathology is evaluated in pubertal / young animals.</li> <li>Thyroid hormones are measured in the Female Pubertal Tier 1 Assay and provide information which is not otherwise available from the cited studies on a chemicals ability to disrupt normal thyroid function. Thyroid hormones were not evaluated in any of the cited studies.</li> <li>Although thyroid histopathology was conducted and no treatment-related changes of the thyroid glands were seen in any of the cited Part 158 studies, it is not clear that thyroid follicular cell height and colloid area were evaluated histologically in any of the cited</li> </ul>	

**Table 8. Evaluation of Data Submitted in Relation to the Female Pubertal Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1450 - Female Pubertal Assay (Rat)</b>	
studies. The Tier 1 pubertal assays include specific instructions on the use of a 5 point grading scale for examination of follicular cell height and colloid area. These instructions include photomicrographs as reference. The 5 point grading scale provides for evaluation of subtle changes that may improve the sensitivity of the histopathological examination.	
<b>Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Female Pubertal Assay using Guideline 890.1450.	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

Chemical: EPTC				PC Code: 041401										
890.1500 - Male Pubertal Assay (Rat)														
1. EDSP Assay Endpoints <sup>1</sup>														
Study Type / Literature Citation	MRID No.	Growth	Age and Weight at PPS	Organ Weights <sup>2</sup>										
				TE	EP	SV	VP	DLP	LABC	TH	LI	KDY	ADR	PIT
ToxCast program	N/A	X	--	--	--	--	--	--	--	--	--	--	--	--
1982 - Two-Generation Reproduction-Rat	00121284	X	--	X	X	--	--	--	--	--	X	X	--	--
1985 - Two-Generation Reproduction- Rats	00161597	X	--	--	--	--	--	--	--	--	--	--	--	--
Developmental Neurotoxicity- Rat	46319101	X	X	--	--	--	--	--	--	--	--	--	--	--
1983 - Developmental Toxicity-Rat	00138919	X	--	--	--	--	--	--	--	--	--	--	--	--
1985 -Developmental Toxicity-Rat	00161598	X	--	--	--	--	--	--	--	--	--	--	--	--
1985 - Developmental Toxicity – Rabbit	00161599	X	--	--	--	--	--	--	--	--	--	--	--	--
1987 - Developmental Toxicity – Rabbit	40442302	X	--	--	--	--	--	--	--	--	--	--	--	--
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	X	--	X	--	--	--	--	--	X	X	X	X	X
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	X	--	X	--	--	--	--	--	--	X	X	--	--
Carcinogenicity – Mouse	00161596	X	--	--	--	--	--	--	--	--	--	--	--	--

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

Chemical: EPTC						PC Code: 041401								
890.1500 - Male Pubertal Assay (Rat)														
1986-Chronic Toxicity – Dog	00161595	X	--	X	--	--	--	--	--	X	X	X	X	X
1987-Chronic Toxicity – Dog	40442301	X	--	X	--	--	--	--	--	X	X	X	X	X
Subchronic Oral Toxicity - Rat	00144651	X	--	X	--	--	--	--	--	--	X	X	--	--
Subchronic Oral Toxicity - Dog	00150327	X	--	X	--	--	--	--	--	X	--	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	X	--	X	--	--	--	--	--	--	--	--	X	--
Study Type/ Literature Citation	MRID No.	EDSP Assay Endpoints: Clinical Chemistry and Pathology <sup>1</sup>												
		Blood Chemistry	Hormones			Histopathology								
			Testosterone	T4	TSH	Epididymides	Testes	Thyroid	Kidney					
ToxCast program	N/A	--	--	--	--	--	--	--	--	--	--	--	--	--
1982 - Two-Generation Reproduction-Rat	00121284	--	--	--	--	X	X	--	--	--	--	--	X	--
1985 - Two-Generation Reproduction- Rats	00161597	X	--	--	--	X	X	--	--	--	--	--	X	--
Developmental Neurotoxicity - Rat	46319101	--	--	--	--	--	--	--	--	--	--	--	--	--
1983 - Developmental Toxicity-Rat	00138919	--	--	--	--	--	--	--	--	--	--	--	--	--
1985 - Developmental Toxicity - Rat	00161598	--	--	--	--	--	--	--	--	--	--	--	--	--
1985 - Developmental Toxicity – Rabbit	00161599	--	--	--	--	--	--	--	--	--	--	--	--	--

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

Chemical: EPTC					PC Code: 041401				
890.1500 - Male Pubertal Assay (Rat)									
1987 - Developmental Toxicity – Rabbit	40442302	--	--	--	--	--	--	--	--
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	X	--	--	--	X	X	X	X
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	X	--	--	--	X	X	X	X
Carcinogenicity – Mouse	00161596	--	--	--	--	X	X	X	X
1986 - Chronic Toxicity – Dog	00161595	X	--	--	--	--	X	X	X
1987 - Chronic Toxicity – Dog	40442301	X	--	--	--	X	X	X	X
Subchronic Oral Toxicity - Rat	00144651	X	--	--	--	X	X	X	X
Subchronic Oral Toxicity - Dog	00150327	X	--	--	--	X	X	X	--
Subchronic Inhalation Toxicity – Rat	00154784	X	--	--	--	--	--	--	X
2. Summary of Study Findings:									
Study Type / Literature Citation	MRID No.	Findings							
ToxCast program	N/A	See discussion below in Section 3.							
1982 - Two-Generation Reproduction - Rat	00121284	No treatment-related effects were observed in the male fertility index, gestation index, gestation length, live birth index, viability index, lactation index, or fetal sex ratio. No treatment-related changes were seen in absolute or relative weights of the testes and epididymides. No treatment-related histopathological lesions were seen in the testes, epididymides, spermatic cord, seminal vesicle, coagulating gland, prostate, urethra or the bulbo-urethral gland in the offspring of either generation.							

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1500 - Male Pubertal Assay (Rat)</b>		
1985 - Two-Generation Reproduction - Rats	00161597	No treatment-related effects were observed in male fertility indices, gestation index, gestation length, live birth index, viability index, lactation index or fetal sex ratio. Organ weights were not evaluated. No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle or prostate in the pups of either generation.
Developmental Neurotoxicity - Rat	46319101	There was no effect on reproductive performance in the mean numbers of live fetuses, resorptions, fetal body weights, or fetal sex ratios. Treatment had no effect on the mean age of attainment of preputial separation for males.
1983 - Developmental Toxicity-Rat	00138919	No treatment-related changes were seen in fetal sex ratio, or soft tissue abnormalities at any dose. There was an increase in post implantation loss and the subsequent reductions in the mean number of viable fetuses at the high dose.
1985 -Developmental Toxicity - Rat	00161598	No treatment-related changes were seen in fetal sex ratio or soft tissue abnormalities at any dose.
1985 - Developmental Toxicity - Rabbit	00161599	No treatment-related changes were seen in number of implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1987 - Developmental Toxicity - Rabbit	40442302	No treatment-related changes were seen in implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
1983 - Chronic Toxicity/Carcinogenicity - Rat	00145004	There were no treatment-related changes in the absolute or relative weights of the testes, thyroid, adrenal or pituitary glands and there were no treatment-related histopathological lesions in the testes, epididymides, prostate, thyroid, adrenal or pituitary glands at any dose level.
1987 - Chronic Toxicity/Carcinogenicity - Rat	40215001	No treatment-related changes were seen in absolute or relative weights of the testes or histopathological lesions in the testes, epididymides, seminal vesicle, prostate, thyroid, adrenal or pituitary glands at any dose level.
Carcinogenicity - Mouse	00161596	No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle, prostate, thyroid, adrenal or pituitary glands. Organ weights were not evaluated.
1986 - Chronic Toxicity - Dog	00161595	No treatment-related changes were seen in absolute or relative weights of the testes, thyroid, adrenal or pituitary glands. There were no treatment-related histopathological lesions in the testes, prostate, thyroid, adrenal or pituitary glands at any dose level.
1987 - Chronic Toxicity - Dog	40442301	No treatment-related changes were seen in absolute or relative weights of the testes, thyroid, adrenal or pituitary glands. No treatment-related histopathological lesions were seen in the testes, epididymides,

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1500 - Male Pubertal Assay (Rat)</b>		
		prostate, thyroid, adrenal or pituitary glands at any dose level.
Subchronic Oral Toxicity - Rat	00144651	No treatment-related changes were seen in absolute or relative weights of the testes nor were there any treatment-related histopathological lesions in the testes, epididymides, seminal vesicle, prostate, thyroid, adrenal and pituitary glands at any dose level.
Subchronic Oral Toxicity - Dog	00150327	No treatment-related changes were seen in absolute or relative weights of the testes or thyroid glands. No treatment-related histopathological lesions were seen in the testes, epididymides, prostate, thyroid, adrenal and pituitary glands at any dose level.
Subchronic Inhalation Toxicity - Rat	00154784	No treatment-related changes were seen in absolute or relative weights of the testes or adrenal gland. Endocrine relevant organs were not examined microscopically. Histopathology was limited to nasal passages, liver, kidney and target tissues.

**3. Agency's Evaluation of the OSRI:**

The submission provided by the test order recipient states that "The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program." "The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. The absence of any effect on serum cholesterol in the whole-animal regulatory studies confirms that EPTC does not cause perturbation of steroidogenesis. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCA section 408(p)(4)." "Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery."

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1500 - Male Pubertal Assay (Rat)</b>	
<p>On review of the OSRI submitted, the Agency noted deficiencies and has remaining questions about the potential for EPTC to disrupt the HPG and HPT axis in males:</p> <ul style="list-style-type: none"> <li>• Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vivo</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Male Pubertal Assay using Guideline 890.1500 (Kavlock and Zenick, 2010).</li> <li>• The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>• The male offspring in the DNT study were evaluated for acceleration or delay in preputial separation; exposure of these animals to EPTC had ceased by the time that this endpoint was evaluated. The Tier 1 Male Pubertal Assay measures exposes the animals during the period during which this endpoint is susceptible to chemical influence. No information was provided to show that ending exposure substantially prior to the normal age of sexual maturation is equivalent to dosing during the critical peri-pubertal period.</li> <li>• Although some of the accessory sex organs weighed in the Male Pubertal Assay were weighed, other such organs were not measured (e.g., levator ani/bulbocavernosus muscle complex) or were not measured appropriately (ventral prostate and dorsolateral prostate weighed separately). It is considered important to evaluate as many of these organs as possible in the same study in which age and weight at preputial separation are measured, and to take these measures at times similar to those specified in the Male Pubertal Assay. This provides more measures for the androgen hormone pathway in the young or developing animals which may be more sensitive than adults; having more measures in these sensitive animals also increases the possibility of identifying subtle or weak endocrine disruptors.</li> <li>• Testosterone which is measured in the Tier 1 Male Pubertal Assay was not measured in any of the cited Part 158 studies.</li> <li>• Organ weight data in the cited Part 158 studies are inadequate because they were obtained in adult/older animals and so do not provide information on the potential for effects at the critical life stage whereas in the Tier 1 Male Pubertal Assay, organ weights are obtained in</li> </ul>	

**Table 9. Evaluation of Data Submitted in Relation to the Male Pubertal Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1500 - Male Pubertal Assay (Rat)</b>	
<p>pubertal /young animals.</p> <ul style="list-style-type: none"> <li>Histopathology data in the cited Part 158 studies are inadequate because they were obtained in adult /older animals and so do not provide information on the potential for effects at the critical life stage whereas in the Tier 1 Male Pubertal Assay, histopathology is evaluated in pubertal / young animals.</li> <li>Thyroid hormones are measured in the Male Pubertal Tier 1 Assay and may provide information which is not otherwise available form the cited studies on a chemicals ability to disrupt normal thyroid function. Thyroid hormones were not evaluated in any of the cited studies.</li> <li>Although thyroid histopathology was conducted, and no treatment-related changes of the thyroid glands were seen in any of the cited Part 158 studies, it is not clear that thyroid follicular cell height and colloid area were evaluated histologically in any of the cited studies. The Tier 1 pubertal assays include specific instructions on the use of a 5 point grading scale for examination of follicular cell height and colloid area. These instructions include photomicrographs as reference. The 5 point grading scale provides for evaluation of subtle changes that may improve the sensitivity of the histopathological examination.</li> </ul>	
<p><b>4. Conclusion:</b></p> <p>Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Male Pubertal Assay using Guideline 890.1500.</p>	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

<sup>2</sup>TE = Testes, EP = Epididymides; SV = Seminal Vesicle; VP= Ventral Prostate; DLP= Dorsolateral Prostate; LABC= levator ani-bulbocavernosus muscle complex; TH= Thyroid; LI= Liver; KDY = Kidney; ADR= Adrenal; PIT= Pituitary

**Table 10. Evaluation of Data Submitted in Relation to the Steroidogenesis Assay**

Chemical: EPTC		PC Code: 041401		
890.1550 - Steroidogenesis Assay (Human Cell Line – H295R)				
1. EDSP Assay Endpoints <sup>1</sup>				
Study Type / Literature Citation	MRID No.	17β- Estradiol Content	Testosterone Content	Cell Viability
ToxCast program	N/A	--	--	--
1982 - Two-Generation Reproduction-Rat	00121284	--	--	--
1985- Two-Generation Reproduction- Rats	00161597	--	--	--
Developmental Neurotoxicity - Rat	46319101	--	--	--
1983 - Developmental Toxicity-Rat	00138919	--	--	--
1985 - Developmental Toxicity-Rat	00161598	--	--	--
1985 - Developmental Toxicity – Rabbit	00161599	--	--	--
1987 - Developmental Toxicity – Rabbit	40442302	--	--	--
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	--	--	--
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	--	--	--
Carcinogenicity – Mouse	00161596	--	--	--
1986 - Chronic Toxicity – Dog	00161595	--	--	--
1987 - Chronic Toxicity – Dog	40442301	--	--	--
Subchronic Oral Toxicity - Rat	00144651	--	--	--
Subchronic Oral Toxicity - Dog	00150327	--	--	--
Subchronic Inhalation Toxicity – Rat	00154784	--	--	--
2. Summary of Study Findings:				
Study Type / Literature Citation	MRID No.	Findings		
ToxCast program	N/A	See discussion below in Section 3.		
Part 158 studies cited above	See Above	The cited <i>in vivo</i> Part 158 mammalian toxicity studies do not measure steroidogenesis.		

**Table 10. Evaluation of Data Submitted in Relation to the Steroidogenesis Assay****Chemical: EPTC****PC Code: 041401****890.1550 - Steroidogenesis Assay (Human Cell Line – H295R)****3. Agency's Evaluation of the OSRI:**

The submission provided by the test order recipient states that “The Agency developed the ToxCast™ program to predict endocrine active agents and profiled over 300 chemicals including EPTC. ToxCast results indicated EPTC has a very low potential for endocrine disruption.”

“The EPTC studies collectively evaluate nearly all relevant biological endpoints of estrogen or androgen mediation of the HPG axis. Multiple studies address most of the endpoints of concern. The few endpoints not directly evaluated are associated with multiple adverse effects; these other effects would have been evident in the regulatory studies from the other monitored parameters.”

“Serum cholesterol is of particular importance as cholesterol is a molecular precursor of all steroid hormones in humans, including estrogens and androgens. Early disruption of steroidogenesis can lead to altered levels of cholesterol and disruptions in cholesterol synthesis can affect steroidogenesis. Cholesterol levels were unaffected in all studies in which it was measured including both male and female rats (90 day oral and inhalation studies and two year studies), and dogs (90 day and one-year studies).”

“The EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program.” “The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCa section 408(p)(4). Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery.”

**Table 10. Evaluation of Data Submitted in Relation to the Steroidogenesis Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1550 - Steroidogenesis Assay (Human Cell Line – H295R)</b>	
<p>On review of the OSRI submitted, the Agency noted deficiencies and has remaining questions about the potential for EPTC to cause perturbation of steroidogenesis.</p> <ul style="list-style-type: none"> <li>• Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vitro</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Steroidogenesis Assay using Guideline 890.1550 (Kavlock and Zenick, 2010).</li> <li>• The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</li> <li>• None of the cited Part 158 studies measures steroidogenesis which is the information that would be obtained by the Tier 1 Steroidogenesis Assay. The argument presented in the explanations submitted to the Agency was that no estrogen or androgen mediated effects were seen in any of the cited studies. A lack of effects on potentially steroid-mediated endpoints in the mammalian <i>in vivo</i> studies cited does not necessarily demonstrate that steroidogenesis has not been affected. Chemicals that disrupt steroidogenesis but do not cause an effect in mammals may nevertheless show effects in other species; consequently it is important to have information concerning direct effects on steroidogenesis.</li> <li>• Cholesterol is the building block for the synthesis of all of the steroid hormones. A change in the synthesis of testosterone or estrogen would not necessarily be reflected in differential levels of cholesterol and this would be an insensitive measure for such downstream events.</li> <li>• None of the cited studies measure key enzymes responsible for steroid synthesis or alterations in estradiol and testosterone concentrations, which is the information that would be obtained by the Tier 1 Steroidogenesis Assay.</li> </ul>	

**Table 10. Evaluation of Data Submitted in Relation to the Steroidogenesis Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1550 - Steroidogenesis Assay (Human Cell Line – H295R)</b>	
<b>4. Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Steroidogenesis Assay using Guideline 890.1550.	

-- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

**Table 11. Evaluation of Data Submitted in Relation to the Uterotrophic Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1600 - Uterotrophic Assay (Rat)</b>		
<b>1. EDSP Assay Endpoints<sup>1</sup></b>		
<b>Study Type / Literature Citation</b>	<b>MRID No.</b>	<b>Uterus Weight</b>
ToxCast program	N/A	--
1982 - Two-Generation Reproduction-Rat	00121284	--
1985 - Two-Generation Reproduction- Rats	00161597	--
Developmental Neurotoxicity - Rat	46319101	--
1983 - Developmental Toxicity-Rat	00138919	--
1985 - Developmental Toxicity-Rat	00161598	--
1985 - Developmental Toxicity – Rabbit	00161599	--
1987- Developmental Toxicity – Rabbit	40442302	--
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	--
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	--
Carcinogenicity – Mouse	00161596	--
1986 - Chronic Toxicity – Dog	00161595	--
1987 - Chronic Toxicity – Dog	40442301	--
Subchronic Oral Toxicity - Rat	00144651	--
Subchronic Oral Toxicity - Dog	00150327	--
Subchronic Inhalation Toxicity – Rat	00154784	--
<b>Study Type / Literature Citation</b>	<b>MRID No.</b>	<b>Findings</b>
ToxCast program	N/A	See discussion below in Section 3.
1982 - Two-Generation Reproduction-Rat	00121284	No treatment-related effects were observed in female fertility index, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio. No treatment-related histopathological

**Table 11. Evaluation of Data Submitted in Relation to the Uterotrophic Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1600 - Uterotrophic Assay (Rat)</b>		
		lesions were seen in the ovaries, uterus, cervix and vagina in the offspring of either generation.
1985 - Two-Generation Reproduction- Rats	00161597	No treatment-related effects were observed in female fertility indices, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio. No treatment-related histopathological lesions were seen in the ovaries, uterus, and vagina. Organ weights were not evaluated.
Developmental Neurotoxicity - Rat	46319101	There was no effect on reproductive performance in the mean numbers of live fetuses, fetal body weights, or fetal sex ratios. No effects were reported in gestation length, viability, or lactation indices. Treatment had no effect on the mean age of attainment of vaginal opening for females.
1983 - Developmental Toxicity-Rat	00138919	No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. There was an increase in post implantation and the subsequent reductions in the mean number of viable fetuses at the high dose.
1985 - Developmental Toxicity-Rat	00161598	No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. The pregnancy rate was 76%, 76% and 72% at the low-, mid- and high dose groups as compared to controls (84%). The decrease in the pregnancy rate is the result of increased post implantation loss at the mid (6.8%) and high (5.3%) dose groups when compared to controls (2.5%) with the increase reaching statistical significance ( $p < 0.05$ ) only for the mid-dose.
1985 - Developmental Toxicity – Rabbit	00161599	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities.
1987 - Developmental Toxicity – Rabbit	40442302	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities.
1983 - Chronic Toxicity/Carcinogenicity – Rat	00145004	No treatment-related changes were seen in absolute or relative weights of

**Table 11. Evaluation of Data Submitted in Relation to the Uterotrophic Assay**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>890.1600 - Uterotrophic Assay (Rat)</b>		
		the ovaries, thyroid, adrenal or pituitary glands not were there any treatment-related histopathological lesions in the ovaries, uterus, cervix, mammary, thyroid, adrenal or pituitary glands at any dose level.
1987 - Chronic Toxicity/Carcinogenicity – Rat	40215001	No treatment-related changes were seen in absolute or relative weights of the ovaries or histopathological lesions in the ovaries, uterus, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level.
Carcinogenicity – Mouse	00161596	No treatment-related histopathological lesions were seen in the ovaries, uterus, cervix, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level. Organ weights were not evaluated.
1986 - Chronic Toxicity – Dog	00161595	No treatment-related changes were seen in absolute or relative weights of the ovaries, thyroid, adrenal or pituitary glands. No treatment-related histopathological lesions were seen in the ovaries, uterus, vagina, mammary gland, thyroid, adrenal or pituitary glands at any dose level.
1987 - Chronic Toxicity – Dog	40442301	No treatment-related changes were seen in absolute or relative weights of the ovaries, thyroid, adrenal or pituitary glands nor were there any treatment-related histopathological lesions in the ovaries, uterus, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level.
Subchronic Oral Toxicity - Rat	00144651	No treatment-related changes were seen in absolute or relative weights of the ovaries and no treatment-related histopathological lesions were seen in the ovaries, uterus, cervix, vagina, mammary gland, thyroid, adrenal and pituitary glands at any dose level.
Subchronic Oral Toxicity - Dog	00150327	No treatment-related changes were seen in absolute or relative weights of the ovaries or thyroid glands. No treatment-related histopathological lesions were seen in the ovaries, uterus, cervix, thyroid, adrenal and pituitary glands at any dose level
Subchronic Inhalation Toxicity – Rat	00154784	No treatment-related changes were seen in absolute or relative weights of the ovaries or adrenal glands. Endocrine relevant organs were not examined. Histopathology was limited to nasal passages, liver, kidney and

**Table 11. Evaluation of Data Submitted in Relation to the Uterotrophic Assay**

Chemical: EPTC	PC Code: 041401
<b>890.1600 - Uterotrophic Assay (Rat)</b>	
	target tissues.
<p><b>3. Agency's Evaluation of the OSRI:</b></p> <p>The submission provided by the test order recipient states that “the EPTC database represents a full assessment of any potential endocrine adverse effect that might be identified in the EDSP Tier I battery. These studies allow for dose-response assessment and subsequent human risk assessment not possible with the Tier I screen and thus, represent a higher tier in the EDSP testing program.” “The diversity of tests and tested species reflects the redundancy sought in the EDSP assays. Altogether, thousands of animals in multiple species have been evaluated for effects on relevant organ weights, gross pathology and histopathology. No effects were observed in either sex to sexual organs or to any endocrine gland (adrenal, pituitary, thyroid). No effects were found that would indicate endocrine-mediated impairment of reproduction function or alteration in developmental progress. The absence of any effect on serum cholesterol in the whole-animal regulatory studies confirms that EPTC does not cause perturbation of steroidogenesis.” “Histopathological effects in nerve and muscle, primarily heart, define the critical regulatory NOAELs at levels significantly lower than any other adverse effects. No biologically relevant effects related to endocrine disruption have been identified following maximally tolerated doses of EPTC. Additional screening for potential endocrine disruption would not result in either lower NOELs or a different risk assessment analysis. Therefore, additional testing for potential endocrine effects will have no impact on the risk assessment analysis for EPTC. Gowan Company believes that collectively, the available data fulfill the requirements of the Endocrine Disruptor Screening Program Data Call-in and that the overwhelming weight-of-the-evidence shows that EPTC is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen or androgen. Therefore, EPTC meets the standard for an exemption under FFDCa section 408(p)(4).” “Gowan Company believes that functional equivalency exists for all the assays in the Tier 1 battery.”</p> <p>On review of the OSRI submitted, the Agency noted deficiencies and has remaining questions about the potential for EPTC to interact with the estrogen pathway.</p> <ul style="list-style-type: none"> <li>• Although the cited ToxCast data may be appropriate for use in priority setting, ToxCast <i>in vitro</i> assays cannot at this time be considered acceptable alternatives to the EDSP Tier 1 <i>in vitro</i> assays. Thus this information is not considered sufficient to satisfy the Test Order requirement for the Uterotrophic Assay using Guideline 890.1600 (Kavlock and Zenick, 2010).</li> <li>• The determination that a chemical either does or does not have the potential to interact with the endocrine system will be made using a weight-of-evidence approach that considers the Tier 1 screening data and or other scientifically relevant information. Chemicals that are</li> </ul>	

**Table 11. Evaluation of Data Submitted in Relation to the Uterotrophic Assay**

<b>Chemical: EPTC</b>	<b>PC Code: 041401</b>
<b>890.1600 - Uterotrophic Assay (Rat)</b>	
<p>identified as having potential to interact with the estrogen, androgen or thyroid hormone systems will proceed to Tier 2 which will identify any adverse effect and establish the quantitative relationship between the dose and the observed endocrine effect of concern for human health and wildlife risk assessment.</p> <ul style="list-style-type: none"> <li>The major difference between the cited studies and the uterotrophic assay is that the cited studies used intact animals. The uterotrophic assay uses the ovariectomized (or immature) female. This difference is critical because ovariectomy removes the major endogenous source of estrogen and thus increases the sensitivity of the uterus to estrogens. As such, the Agency has remaining questions regarding the sensitivity of the uterus to estrogens in female animals exposed to the chemical.</li> </ul>	
<p><b>4. Conclusion:</b> Based on the deficiencies and unanswered questions listed above, the data cited as OSRI did not satisfy the requirement for the Uterotrophic Assay using Guideline 890.1600.</p>	

<sup>1</sup> -- = not measured; X = indicates the endpoint was measured in the assay but does not indicate whether or not it satisfies the data requirement of the test order. See section 3 below for a detailed explanation; N/A = not applicable

### III. Summary of studies cited in the OSRI submission that were considered in the EDRT's evaluation

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
00121284 40420408	<p><u>Study Type:</u> Two-Generation Reproduction</p> <p><u>Classification:</u> Minimum</p> <p><u>Year:</u> 1982</p> <p><u>Species:</u> Rat</p> <p><u>Strain:</u> Crl:CD(SD) Br</p> <p><u>Sex:</u> Male and Female</p> <p><u>Age at Initiation:</u> 6-8 weeks</p>	<p><u>Dose levels tested:</u> 0, 2, 10 or 50 mg/kg/day in the diet for two generations: from 40 days of age with mating occurring at day 130 and again at day 186. Pups from the second litter (F1b) were treated with EPTC from weaning and continued through termination at 230 days with mating occurring at 100 and 155 days of age.</p> <p><u>Reproductive toxicity:</u> No effects were observed in the reproductive performances (male or female fertility indices, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio).</p> <p><u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes and epididymides in any generation.</p> <p><u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, spermatic cord, seminal vesicles, coagulating gland, prostate, urethra, bulbo-urethral gland, ovaries, uterus, cervix and vagina in the offspring of either generation.</p>
00161597	<p><u>Study Type:</u> Two-Generation Reproduction</p> <p><u>Classification:</u> Minimum</p> <p><u>Year:</u> 1985</p> <p><u>Species:</u> Rat</p> <p><u>Strain:</u> Crl:CD(SD) Br</p>	<p><u>Dose levels tested:</u> 0, 2.5, 10 or 40 mg/kg/day in the diet for two generations: the F0 animals were treated for 10 weeks prior to producing the F1 generation and the F1 parental animals were treated for 10 weeks prior to producing the F2 litters</p> <p><u>Reproductive toxicity:</u> No treatment-related effects were observed in male or female fertility indices, gestation index, gestation length, live birth index, viability index, lactation index, parturition, or fetal sex ratio.</p>

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
	<u>Sex:</u> Male and Female  <u>Age at Initiation:</u> 5 weeks	<u>Organ weights:</u> Not evaluated.  <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle, prostate, ovaries, uterus, and vagina.
46319101	<u>Study Type:</u> Developmental Neurotoxicity  <u>Classification:</u> Minimum  <u>Year:</u> 2004  <u>Species:</u> Rat  <u>Strain:</u> Wistar  <u>Sex:</u> Pregnant females  <u>Age at initiation:</u> 10-12 weeks	<u>Dose levels tested:</u> 0, 7.6, 21.9 or 67.2 mg/kg/day in the diet from gestation day 7 through lactation day 23.  There was no effect on reproductive performance in the mean numbers of live fetuses, fetal body weights, or fetal sex ratios.  No effects were reported in gestation length, viability, or lactation indices.  Treatment had no effect on the mean age of attainment of vaginal opening for females or preputial separation for males.
00138919	<u>Study Type:</u> Developmental Toxicity  <u>Classification:</u> Minimum  <u>Year:</u> 1983  <u>Species:</u> Rat  Strain: Sprague Dawley  <u>Sex:</u> Pregnant female  <u>Age at Initiation:</u> Not reported	<u>Dose levels tested:</u> 0, 30, 100, or 300 mg/kg/day in corn oil via gavage from days 6 through 15 of gestation; dams were sacrificed on day gestation day 20.  No treatment-related changes were seen in pregnancy rate, numbers of corpora lutea, fetal sex ratio, or soft tissue abnormalities at any dose. There was an increase in post implantation and the subsequent reductions in the mean number of viable fetuses at the high dose.

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
00161598	<p><u>Study Type:</u> Developmental Toxicity</p> <p><u>Classification:</u> Minimum</p> <p><u>Year:</u> 1985</p> <p><u>Species:</u> Rat</p> <p><u>Strain:</u> CrI:COBS (SD) BR</p> <p><u>Sex:</u> Pregnant female</p> <p><u>Age at Initiation:</u> Not reported</p>	<p><u>Dose levels tested:</u> 0, 30, 100, or 300 mg/kg/day in 1% aqueous methyl cellulose via gavage from days 6 through 15 of gestation; dams were sacrificed on day gestation day 20.</p> <p>No treatment-related changes were seen in pregnancy rate, fetal sex ratio, or soft tissue abnormalities at any dose. The pregnancy rate was 76%, 76% and 72% at the low-, mid- and high dose groups as compared to controls (84%). The decrease in the pregnancy rate is the result of increased post implantation loss at the mid (6.8%) and high (5.3%) dose groups when compared to controls (2.5%) with the increase reaching statistical significance (<math>p &lt; 0.05</math>) only for the mid-dose.</p>
00161599	<p><u>Study Type:</u> Developmental Toxicity</p> <p><u>Classification:</u> Minimum</p> <p><u>Year:</u> 1985</p> <p><u>Species:</u> Rabbit</p> <p><u>Strain:</u> New Zealand</p> <p><u>Sex:</u> Pregnant females</p> <p><u>Age at Initiation:</u> Sexually active</p>	<p><u>Dose levels tested:</u> 0, 30, 100 or 300 mg/kg/day in 1% aqueous methyl cellulose via gavage on days 6 through 18 of gestation; does were sacrificed on gestation day 29.</p> <p>No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.</p>
40442302	<p><u>Study Type:</u> Developmental Toxicity</p>	<p><u>Dose levels tested:</u> 0, 5, 40 or 300 mg/kg/day in corn oil via gavage on days 7 through 19 of gestation; does were sacrificed on gestation day 29.</p>

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
	<u>Classification:</u> Minimum <u>Year:</u> 1987 <u>Species:</u> Rabbit <u>Strain:</u> New Zealand <u>Sex:</u> Pregnant females <u>Age at Initiation:</u> Not reported	No treatment-related changes were seen in pregnancy rate, number of corpora lutea, implantation sites, number of live fetuses/litter, the extent of resorptions/implantations, fetal sex ratio, or soft tissue abnormalities at any dose.
00145004 00146311	<u>Study Type:</u> Chronic Toxicity/ Carcinogenicity <u>Classification:</u> Minimum <u>Year:</u> 1983 <u>Species:</u> Rat <u>Strain:</u> Crl-CD <u>Sex:</u> Male and Female <u>Age at Initiation:</u> 5 weeks	<u>Dose levels tested:</u> 0, 5, 25 or 125 mg/kg/day in the diet for 104 weeks. <u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes, ovaries, thyroid, adrenal or pituitary glands at any dose level. <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, prostate, ovaries, uterus, cervix, mammary gland, thyroid, adrenal or pituitary glands at any dose level.
40215001	<u>Study Type:</u> Chronic Toxicity/ Carcinogenicity <u>Classification:</u> Minimum <u>Year:</u> 1987	<u>Dose levels tested:</u> 0, 9, 18, 36 or 72 mg/kg/day in the diet for 104 weeks. <u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes or ovaries at any dose level. <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle, prostate, ovaries, uterus, vagina, mammary, thyroid, adrenal or

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
	<u>Species:</u> Rat <u>Strain:</u> Crl:CD(SD) Br <u>Sex:</u> Male and Female <u>Age at Initiation:</u> Not reported	pituitary glands at any dose level.
00161596	<u>Study Type:</u> Carcinogenicity <u>Classification:</u> Minimum <u>Year:</u> 1986 <u>Species:</u> Mouse <u>Strain:</u> CD-1 (ICR) BR <u>Sex:</u> Male and Female <u>Age at Initiation:</u> 5 weeks	<u>Dose levels tested:</u> 0, 30, 90, or 270 mg/kg/day in the diet for 78 weeks. <u>Organ weights:</u> Not evaluated. <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle, prostate, ovaries, uterus, cervix, vagina, mammary, thyroid, adrenal or pituitary glands at any dose level.
00161595	<u>Study Type:</u> Chronic Toxicity <u>Classification:</u> Minimum <u>Year:</u> 1986 <u>Species:</u> Dog <u>Strain:</u> Beagle <u>Sex:</u> Male and Female	<u>Dose levels tested:</u> 0, 5.57, 17.27, or 48.51 mg/kg/day for males and 0, 6.08, 17.39, or 54.66 mg/kg/day for females in the diet for 1-year <u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes, ovaries, thyroid, adrenal or pituitary glands at any dose level. <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, prostate, ovaries, uterus, vagina, mammary gland, thyroid, adrenal or pituitary glands at any dose level.

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
	<u>Age at initiation:</u> 5 months	
40442301	<u>Study Type:</u> Chronic Toxicity  <u>Classification:</u> Minimum  <u>Year:</u> 1987  <u>Species:</u> Dog  <u>Strain:</u> Beagle  <u>Sex:</u> Male and Female  <u>Age at Initiation:</u> 7 months	<u>Dose levels tested:</u> 0, 1, 8, or 60 mg/kg/day in gelatin capsules for 1-year  <u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes, ovaries, thyroid, adrenal or pituitary glands at any dose level.  <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, prostate, ovaries, uterus, vagina, thyroid, adrenal or pituitary glands at any dose level.
00144651	<u>Study Type:</u> Subchronic Oral Toxicity  <u>Classification:</u> Minimum  <u>Year:</u> 1984  <u>Species:</u> Rat  <u>Strain:</u> CrI: CD (SD) BR  <u>Sex:</u> Male and Female  <u>Age at Initiation:</u> 38 days	<u>Dose levels tested:</u> 0, 18, 36, 72 or 120mg/kg/day in the diet for 13 weeks.  <u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes or ovaries at any dose level.  <u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, seminal vesicle, prostate, ovaries, uterus, cervix, vagina, mammary gland, thyroid, adrenal and pituitary glands at any dose level.

Chemical: EPTC		PC Code: 041401
MRID No.	Citation in OSRI	Selected Endocrine Related Findings
00150327	<p><u>Study Type:</u> Subchronic Oral Toxicity</p> <p><u>Classification:</u> Minimum</p> <p><u>Year:</u> 1985</p> <p><u>Species:</u> Dog</p> <p><u>Strain:</u> Beagle</p> <p><u>Sex:</u> Male and Female</p> <p><u>Age at Initiation:</u> 6 months</p>	<p><u>Dose levels tested:</u> 0, 5, 15, or 45 mg/kg/day in the diet for 13 weeks.</p> <p><u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes, ovaries or thyroid glands at any dose level.</p> <p><u>Histopathology:</u> No treatment-related histopathological lesions were seen in the testes, epididymides, prostate, ovaries, uterus, cervix, thyroid, adrenal and pituitary glands at any dose level</p>
00154784	<p><u>Study Type:</u> Subchronic Inhalation Toxicity</p> <p><u>Classification:</u> Minimum</p> <p><u>Year:</u> 1985</p> <p><u>Species:</u> Rat</p> <p><u>Strain:</u> Sprague Dawley</p> <p><u>Sex:</u> Male and Female</p> <p><u>Age at Initiation:</u> 7-8 weeks</p>	<p><u>Dose levels tested:</u> 0, 8.3, 58 or 290 mg/m<sup>3</sup>, 6 hours/day, 5 days/week for 13 weeks.</p> <p><u>Organ weights:</u> No treatment-related changes were seen in absolute or relative weights of the testes, ovaries or adrenal glands.</p> <p><u>Histopathology:</u> Endocrine relevant organs were not examined. Histopathology was limited to nasal passages, liver, kidney and target tissues.</p>

**IV. Studies cited in the OSRI but were rejected in the EDRT's weight of evidence evaluations.**

<b>Chemical: EPTC</b>		<b>PC Code: 041401</b>
<b>MRID No.</b>	<b>Study Type or Literature Citation</b>	<b>Reason for not using the study</b>
42921901	Subchronic Neurotoxicity – Rat	The objective of this study was to evaluate the neurotoxic potential of EPTC and therefore, the evaluation parameters were limited to the nervous system. No endocrine relevant organs were evaluated.
00022101	1-Year Status of the Combined Chronic Toxicity/ Carcinogenicity-Rat	This was an interim (1-year) report of a Combined Chronic Toxicity/ Carcinogenicity study in rats (40215001). Data from this interim period were included in the final analyses/evaluation of the study.
00022100	24-Month Mouse Oncogenicity	This study conducted in 1978 did not adhere to the Good Laboratory Practices nor was conducted according to the 1984 Subdivision Guideline protocol.

## V. Bibliography of Existing Data Cited in the OSRI

### (i) Part 158 Studies

<u>MRID</u>	<u>Citation</u>
00022100	Goldenthal, E (1978) Lifetime Oral Study in Mice. International Research and Development Corporation. Report No. 153-011.
00022101	Trutter, J. (1978) 54-Week Feeding Study in Rats: Eptam Technical. Hazleton Laboratories America, Inc. Report No.: 132-131
00121284	Minor, J.; Downs, J.; Zwicker, G.; et al. (1982) A Two-generation Rat Reproduction Study with Eptam Technical: T-10123. (Unpublished study received 1982 under unknown admin. no.; CDL: 249077-A)
00138919	Nemec, M.; Rodwell, D.; Kopp, S.; et al. (1983) A Teratology Study in Rats with EPTAM: Project No. WIL-27013; T-11753. Final rept. (Unpublished study received Feb 2, 1984 under unknown admin. no.; prepared by WIL Research Laboratories, Inc., submitted by Stauffer Chemical Co., Richmond, CA; CDL:252322-A)
00146311	Goldenthal, E. (1985) Two Year Oral Toxicity/Oncogenicity Study in Rats: Addendum to the Final Report: Report No. 153-100. Unpublished study prepared by International Research and Development Corp. 70 p.
00144651	Tisdell, M. (1983) Thirteen-week Subchronic Study in Rats with EPTC: Final Report: Study No. 6100-105. Unpublished study prepared by Hazleton Laboratories America, Inc. 650 p.
00145004	Warner, M. (1983) Two Year Oral Toxicity/Oncogenicity Study in Rats [with R-1608]. Unpublished study prepared by International Research and Development Corp. 1133 p.
00150326	Tisdell, M. (1985) One Year Status Report: Two-year Oral Feeding Study of the Oncogenicity and Chronic Toxicity of EPTC in Rats: Study No. 6100-106. Unpublished study prepared by Hazleton Laboratories America, Inc. 182 p.
00150327	Daly, I. (1985) A Three Month Subchronic Oral Dietary Toxicity Study of EPTC in Beagle Dogs: Project No. 83-2781. Unpublished study prepared by Bio/dynamics Inc. 475 p.
00154784	Scott, J. (1985) Subchronic Inhalation Toxicity of Eptam in Rats. Stauffer Chemical Company Report No. T-10422
00161595	Dickie, B.B (1986) One-Year Oral Feeding Study of the Chronic Toxicity of EPTC in Dogs. Hazleton Laboratories America, Inc. Report No. 6100-109

- 00161596 Tisdell, M. (1985) Oncogenicity Study in Mice with EPTC: Final Report: Study No. 6100-104. Unpublished study prepared by Hazleton Laboratories America, Inc. 1244 p.
- 00161597 Mackenzie, K. (1986) Two-generation Reproduction Study with EPTC in Rats: Report: Study No. 6100-108. Unpublished study prepared by Hazleton Laboratories America, Inc. 1192 p.
- 00161598 James, P.; Smith, J.; John, D. (1985) Effect of EPTC on Pregnancy of the Rat: PPG 19/851002. Unpublished study prepared by Huntingdon Research Centre Ltd. 104 p.
- 00161599 James, P., Smith, J., Masters, R., and Offer, J. (1985) Effect of EPTC on Pregnancy of the Rabbit. Unpublished study prepared by Huntingdon Research Centre Ltd. PPG 14 & 18/85601. 112 p.
- 40420408 Zwicker, G.; Minor, J. (1987) A Two-generation Rat Reproduction Study with EPTAM Technical: T-10123: Addendum to Final Report-Histopathology. Unpublished study prepared by Stauffer Chemical Co. 102 p.
- 40215001 Dickie, B. (1987) Two-year Oral Feeding Study of the Oncogenicity and Chronic Toxicity of EPTC in Rats: Final Report: HLA Study No. 6100-106. Unpublished study prepared by Hazleton Laboratories America, Inc. 4,102 p.
- 40442301 Sprague, G.; Taylor, D. (1987) One-year Oral Toxicity Study with Eptam Technical in Dogs: T-12723: Final Report. Unpublished study prepared by Stauffer Chemical Co. 450 p.
- 40442302 Gilles, P. (1987) A Teratology Study in Rabbits with Eptam Technical: T-12982 Final Report. Unpublished study prepared by Stauffer Chemical Co. 219 p.
- 43230901 Tinston, D. (1995) EPTC: Subchronic Neurotoxicity Study in Rats: Lab Project Number: CTL/P/3930: PR0929. Unpublished study prepared by Zeneca Central Toxicology Lab. 364 p.
- 46319101 Lees, D. (2004) EPTC: Developmental Neurotoxicity Study in Rats. Project Number: CTL/RR0926/REGULATORY/REPORT, RR0926, CTL/RR0926/REG/REPT. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 2418 p.
- 46554301 Temple, D., Martin K., Beavers, K. and Jaber, M. (2005): A Reproduction Study with the Mallard. Wildlife International, Ltd, Project Number:334/112.
- 46554302 Temple, D., Martin K., Beavers, K. and Jaber, M. (2005): A Reproduction Study with the Northern Bobwhite. Wildlife International, Ltd, Project Number: 334/111.

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13544

# R188209

**Chemical Name:** Carbamothioic acid, dipropyl-, S-ethyl ester

**PC Code:** 041401

**HED File Code:** 21220 EDRT Reviews

**Memo Date:** 11/22/2010

**File ID:** 00000000

**Accession #:** 000-00-0136

**HED Records Reference Center**  
11/30/2010